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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/068,426	SHAW ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-9,11-14,20-22,27,54-60 and 63-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-9,11-14,20-22,27,54-60 and 63-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/20/04 has been entered.

2. Claims 1, 3, 5-9, 11-14, 20-22, 27, 54-60 and 63-66 are pending and under examination.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3, 5-9, 11-14, 20-22, 27 and 54-62 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the fusion polypeptide comprising SEQ ID NO:1 or SEQ ID NO:5 for inhibiting platelet aggregation; does not reasonably provide enablement for any polypeptide comprising a first polypeptide operably linked to a second polypeptide, wherein the first polypeptide **comprises** any polypeptide sequence with "at least 85% homology" to an extracellular portion of a glycoprotein Ibα polypeptide of SEQ ID NO:1, provided said glycoprotein Ibα polypeptide includes an amino acid other thatn glycine at position 233 or other than ethionine at position 239 relative to the amino acid sequence of a wild-type GPIbα polypeptide and said first polypeptide binds a polypeptide selected from the group consisting of leukocyte integrin Mac-1 polypeptide, von Willebrand factor, thrombin and P-selectin; and wherein the second polypeptide **comprises** at least any region of an immunoglobulin heavy chain polypeptide in claim 1; wherein said first polypeptide binds to at least two of the polypeptides selected from the group consisting of leukocyte integrin Mac-1 polypeptide, von Willebrand factor, thrombin and P-selectin in claim 3, wherein said fusion polypeptide is more resistant to proteolysis than a wild-type GP Ibα polypeptide in claim 6, wherein said first polypeptide binds with higher affinity to a von Willebrand factor polypeptide than a wild type glycoprotein Ibα polypeptide binds to said von Willebrand factor polypeptide in claim 7, wherein said first polypeptide comprises at least one of the amino acid substitutions G233V or M239V relative to the amino acid sequence of a wild-type GPIbα polypeptide in claim 8, wherein said first polypeptide comprises the amino acid substitutions G233V or M239V relative to the amino acid sequence of a wild-type GPIbα polypeptide in claim 9, wherein said second polypeptide comprises an Fc-region of an immunoglobulin heavy chain in claim 11; any multimeric polypeptide comprising the fusion polypeptide of claim 1 in claim 21, wherein said multimeric polypeptide is a dimmer in claim 22, a pharmaceutical composition comprising the fusion polypeptide of claim 1 in claim 27, wherein said first polypeptide binds at least three

polypeptides selected from the group consisting of leukocytes integrin Mac-1 polypeptide, von Willebrand factor, thrombin and P-selectin in claim 54, wherein said first polypeptide binds leukocyte integrin Mac-1 polypeptide, von Willebrand factor, thrombin and P-selectin in claim 55, wherein said first polypeptide binds leukocyte integrin Mac-1 polypeptide in claim 56, wherein said first polypeptide binds von Willebrand factor in claim 57, wherein said first polypeptide binds thrombin in claim 58, wherein said first polypeptid4e binds P-selection in claim 59; any fusion polypeptide comprising a fist polypeptide operably linked to a second polypeptide wherein the first polypeptide consists essentially of a polypeptide sequence with at least 85% homology to an extracellular portion of a glycoprotein Ibα polypeptide of SEQ ID NO:1 and said first polypeptide binds von Willebrand factor polypeptide and wherein said second polypeptide consists essentially of an immunoglobulin heavy chain polypeptide, wherein said immunoglobulin heavy chain polypeptide comprises a Fc region in claim 60. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 11/04/03.

The claims now recite mutant GPIbα polypeptide that binds to either leukocyte integrin Mac-1 polypeptide, VWF, thrombin and P-selectin. While the binding sites for vWF, Mac-1, P-selectin and α-thrombin are contained within the extracellular N-terminal 282 residues of GPIb α, the specific mutants recited in the claims have been shown to only bind to VWF. The specification does not provide guidance as to how the specific GPIbα mutations would still lead to the binding the other molecules.

Applicant's arguments, filed 8/20/04, have been fully considered, but have not been found convincing.

Applicant submits that the specification provides detailed teachings for making and using the claimed polypeptides. Applicant submits that methods for detecting binding of a GPIbα protein to a ligand such as those recited in clim1 are also well known in the art. Applicant submits that one of ordinary skill in the art can readily practice the full scope of the invention now claimed using the teachings of the specification.

The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, the enablement issues of making the protein still remain because the specification does not teach and provide sufficient guidance as to which amino acid of SEQ ID NO:1 would have been altered (besides amino acid at position 233 and position 239) such that the resultant polypeptide would have retained the function of inhibiting platelet aggregation. In addition, variation up to 15% of SEQ ID NO: 1 (81^{15}) provide a range of activities, not all which are necessarily predictive of binding to leukocyte integrin Mac-1 polypeptide, von Willebrand factor, thrombin and P-selectin. Without detailed direction as to which amino acid sequences are essential to the function of the polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of amino acid sequences encompassed by the instant

claims would share the ability to bind leukocyte integrin Mac-1 polypeptide, von Willebrand factor, thrombin and P-selectin, other than the amino acid of SEQ ID NO:5.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over in Lopez JA et al (Proc Natl Acad Sci U S A. 84:5615-5619, 1987) view of U.S. Patent No. 6,277,975.

Lopez *et al* teach a 626 amino acid glycoprotein Ibα (including the signal sequence of 16 amino acids) that is a platelet receptor for von Willebrand factor comprising a region of a glycoprotein Ibα polypeptide which includes an extracellular portion. The vWf and thrombin binding domain of GP Ibα, which contains seven tandem repeats of the conserved leucine-rich sequence resides within the amino terminus of the molecules (see page 5618, figure 5 and abstract in particular). The N-terminal region (aa 1-318 of SEQ ID NO:1) is 100% identical to the first polypeptide of the fusion polypeptide (see sequence alignment in particular). Finally Lopez et al teach that adhesion requires that binding of platelet membrane glycoprotein Ib (GPIb) to von Willebrand factor (vWF) following the binding of vWF to the subendothelial matrix (see pg 5615, 1st paragraph in particular)

The claimed invention differs from the reference teachings only in that SEQ ID NO: 1 comprises a region of an immunoglobulin heavy chain polypeptide.

The `975 patent teaches the P-selectin ligand fusion protein comprises a 313 amino acid sequence (see reference SEQ ID NO: 36 in particular) comprising Fc portion of a human of IgGγ1 (column 11, lines 40-41 in particular) with 100% homology with amino acids 318-544 of claimed SEQ ID NO: 1 (see sequence alignment in particular). The `975 patent further teaches that Fc portion of native or mutated immunoglobulin sequences for conferring desirable qualities such as longer half-life or reduced immunogenicity (see column 10 lines 37-40 in particular). Finally, the `975 patent teaches pharmaceutical compositions comprising the P-selectin ligand proteins (column 4, lines 48-50 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to link the glycoprotein Ibα region taught by Lopez *et al* with Fc portion of a human IgGγ1 taught by the `975 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because gpIbα is a platelet receptor for von Willebrand factor which is require for adhesion of platelets during blood vessel injury and the Fc portion of native or mutated immunoglobulin sequences conferring desirable qualities such as longer half-life or reduced immunogenicity as taught by the `972 patent and the vWf-binding domain of GP Ibα resides within the amino terminus of the molecule taught by Lopez et al.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 8/20/04, have been fully considered, but have not been found convincing.

Applicant argues that there is no teaching or suggestion in either reference of a polypeptide with the claimed GPIbα sequence that includes an amino acid other than glycine at position 233 or an amino acid other than methionine at position 239 relative to the amino acid sequence of a wild type polypeptide. Applicant submits that Lopez et al teach a wild-type GPIba but not a protein or fusion protein that includes the GPIbα polypeptide sequence now claimed.

However, claims 63-64 recite the wild-type protein taught by Lopez et al. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to make a fusion protein using the GPIbα region taught by Lopez et al with the Fc portion of a human Igggl taught by the `975 patent because gpIbα is a platelet receptor for von Willebrand factor which is require for adhesion of platelets during blood vessel injury and the Fc portion of native or mutated immunoglobulin sequences conferring desirable qualities such as longer half-life or reduced immunogenicity as taught by the `972 patent and the vWf-binding domain of GP Ibα resides within the amino terminus of the molecule taught by Lopez et al

8. Claims 1, 3, 6-9, 11-14, 21-22, 27, 54-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over in Miura *et al* (J Biol Chem. 275:7539-7546) view of U.S. Patent No. 6,277,975.

Miura *et al* teach a GPIbα-calmodulin fusion protein (aa residues His^{1}-Val^{289}) of GPIbα (GPIbα-CaM), Ibαwt, Ibα233V, Ibα239V and Ibα233V239V (as in instant claim 9 and claimed SEQ ID NO:5) (see page 7540 under Expression and purification of GPIbα proteins in particular). Miura et al further teach GPIbα mutaions G233V and M239V with increase in affinity of VWF A1 for

GPIbα(M239V)-CaM and GPIbα(M233V)-CaM (see abstract in particular). Miura *et al* teach that platelet adhesion requires the binding of VWF to the platelet membrane glycoprotein Ib-IX (extracellular portion) and the binding site for VWF is in the N-terminal 293 residues of GPIbα. Finally, Miura et al teach the GPIba-CaM (or variant) in Tris-HCl buffer. (see page 7539, right column, 1st paragraph in particular). Miura et al teach that the kinetic parameters of VWF-Gpib interactions are central to the mechanism by which VWF mediates platelet adhesion under conditions of high wall shear stress. Miura et al teach that inclusion of the mutation G233V increases the adhesion of GPIbα (1-302) binding to VWF and increases the adhesion of GPIba-(302)-coated latex beads to VWF (see pg 7545, 1st col. 1st ¶ in particular). Further, Miura et al teach that the distinct platelet-type pseudo-VWD mutation M239V increased the affinity of binding slightly more. Furthermore, the effects of these mutations GPIbα(G233V/M239V)-CaM were not additive (pg 7546 1st ¶). Miura et al concluded that such a foundation can facilitate the development of antithrombotic agents that target the initial step of platelet adhesion (pg 7546, last ¶ in particular).

The claimed invention differs from the reference teachings only by the recitation of that the fusion protein, wherein said first polypeptide is more resistant to proteolysis than a wild-type GP Ibα1 polypeptide in claim 6, wherein the said second polypeptide comprises an Fc region of an immunoglobulin heavy chain in claim 11, wherein said second polypeptide has less effector function that the effector function of a Fc region of a wild-type immunoglobulin heavy chain in claim 12, wherein said second polypeptide binds with low or no affinity to a Fc receptor in claim 13, wherein said second polypeptide binds with low or no affinity to complement protein C1q in claim 14, a multimeric polypeptide comprising the fusion protein in claim 21, wherein the multimeric polypeptide is a dimmer in claim 22. wherein the first polypeptide binds at least three polypeptides selected from leukocyte integrin Mac-1 polypeptide, von Willebrand factor, thrombin and p-selectin in claims 54, wherein the firs polypeptide binds leukocyte integrin Mac-1 polypeptide, von Willebrand factor, thrombin and P-selectin in claim 55, wherein said first polypeptide binds leukocyte integrin Mac-1 polypeptide in claim 56, wherein said first polypeptide binds von Willebrand factor in claim 57, wherein said first polypeptide binds thrombin in claim 58, wherein said first polypeptide binds P-selectin in claim 59.

The `975 patent teaches the P-selectin ligand fusion protein comprises a 313 amino acid sequence (see reference SEQ ID NO: 36 in particular) comprising Fc portion of a human of IgGγ1 (column 11, lines 40-41 in particular) with 100% homology with amino acids 318-544 of claimed SEQ ID NO: 1 (see sequence alignment in particular). The `975 patent further teaches that Fc portion of native or mutated immunoglobulin sequences for conferring desirable qualities such as longer half-life or reduced immunogenicity (see column 10 lines 37-40 in particular). Finally, the `975 patent teaches pharmaceutical compositions comprising the P-selectin ligand proteins (column 4, lines 48-50 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Calmodulin peptide taught by Miura *et al* with Fc portion of a human IgGγ1 taught by the `975 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because inclusion of the mutation G233V increases the adhesion of GPIbα (1-302) binding to VWF and increases the adhesion of GPIba-(302)-coated latex beads to VWF. Further, the distinct platelet-type pseudo-VWD mutation M239V increased the affinity of binding slightly more, while the effects of these mutations GPIbα(G233V/M239V)-CaM were not additive (6 fold). Further, Fc portion of native or mutated immunoglobulin sequences conferring desirable qualities such as longer half-life or reduced immunogenicity as taught by the `972 patent.

Claim 6 is included because the claimed and reference first polypeptide are the same in the absence of evidence to the contrary and therefore, the claimed limitation of more resistant to proteolysis than wild-type GPIbα1 polypeptide is considered inherent properties.

The claimed functional limitation of claims 12-14, 21-22 would be expected properties of the referenced Fc region of a human of IgGγ1 because the claimed and reference Fc region are 100% identical. Further, binding of the first polypeptide to leukocyte integrin Mac-1 polypeptide, von Willebrand factor, thrombin and P-selectin of claims 54-59 is inherent property of the 1st polypeptide. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 8/20/04, have been fully considered, but have not been found convincing.

Applicant argues in conjunction with case law that in order to establish a case of obviousness by combining references there must be a suggestion or motivation for such a combination originating within the references themselves. Further, Applicant argues that the resulting combination must arrive at the claimed invention considered as a whole. Applicant contends that there is no suggestion or expectation of success in the combination of Miura and the `975 patent of a fusion polypeptide that includes a GPIbα variant polypeptide component, i.e., a GPIba polypeptide portion that has an amino acid other thatn methionine at position 233 or other than methionine at position 239 relative to the amino acid sequence of wild-type human GPIbα, and a portion of an immunoglobulin polypeptide.

Contrary to Applicant assertions Miura et al teachings provide advantages and motivation to establish a case of obviousness for example Miura et al teaches the GPIbα mutations G233V and/or M239V increases the affinity of GPIbα-(1-302) binding to VWF and increases the adhesion of GPIbα-(1-302)-coated latex beads to VWF (pg 7545, 1st col., 1st ¶) which can facilitate the development of antithrombotic agents that target the initial step of platelet adhesion (see pg 7646, 1st col., last ¶).

Applicant submits that while Miura et al describe GPIbα polypeptide wit the G233V and M239V mutations, however, Miura et al reference teaches that " the GPIbα mutants G233V and M239V cause platelet-type pseudo-von willebrand disease". Applicant argues that Miura et al lack any other teaching that GPIba mutants with these sequences would nevertheless be a useful as a therapeutic agent.

Contrary to applicant assertions Miura et al taught "such a foundation could facilitate the development of antithrombotic agents that target the initial step of platelet adhesion". Therefore, Miura et al suggested that efficient platelet tethering and rolling using GPIbα mutants can facilitate the development of thereapeutic agent that target the initial step of platelet adhesion (pg 7546, last ¶).

Applicant further argues that the Examiner relied on the `975 patent to provide a motivation for making the claimed polypeptide, however, such motivation would only provide motivation for making a fusion protein that would be used as a therapeutic agent. Applicant submits that there is no teaching or suggestion in Miura et al that its variant GPIbα polypeptides could be used to treat a disease or condition. Applicant concluded that the artisan would have no motivation for making a fusion protein by combining the variant GPIbα disclosed in Miura with the IG polypeptides disclosed in the `975 patent. Applicant states that the artisan would have no motivation to prolong the half life or lessen the immunogenicity of a variant GPIbα polypeptide for which Miura itself gives no reason to think has a therapeutic use. Applicant further argues that because the variant polypeptides are associated with a disease, there is no expectation that combining the variant GPIbα polypeptides with the `975 immunoglobulin sequences would be successful for making a therapeutic polypeptide.

Again, Miura et al taught "such a foundation could facilitate the development of antithrombotic agents that target the initial step of platelet adhesion". Therefore, Miura et al suggested that efficient platelet tethering and rolling using GPIbα mutants can facilitate the development of thereapeutic agent that target the initial step of platelet adhesion (pg 7546, last ¶). Such teachings provide a motivation to make the claimed fusion polypeptide of GPIbα mutants. Regarding Applicant argument that the variant polypeptides are associated with a disease, ant that there is no expectation that combining the variant GPIba polypeptide with the `975 immunoglobulin sequences would be successful for making a therapeutic polypeptide. The Examiner notes that the test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art . In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the GPIbα mutations cause platelet-type pseudo-van willebrand disease (type 2B) due to increased platelet tethering to VWF, that would suggest to one of ordinary skill in the art to use the claimed GPIbα mutants polypeptides as a therapeutic agent to permit platelet translocation/or to prevent platelet aggregation. A competing GPIbα variant in type 2B platelet-type pseudo-VWD would lead to a decrease in binding of platelet to the VWD.

Applicant traverses the rejection on the ground that no motivation or expectation of success in replacing the calmodulin moiety in the GPIbα calmodulin fusion protein described in Miura et al with an Ig moiety described in the `975 patent. Applicant submits that Miura et al report that the calmodulin is present to facilitate purification of this fusion protein on phenothiazine derivative W-7 agarose column. Applicant submits that one of ordinary skill in the art would not replace the calmodulin moiety in Miura fusion protein with an immunoglobulin moiety because such a substitutio would render the fusion proeitn unusable for the purpose Miura requires, i.e., capture on a phenothiazine derivative W-7 agarose column.

The examiner notes that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See MPEP 2145.

9. Claims 1, 3, 6-9, 11-14, 21-22, 27, 54-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over in USP 6,177,059 view of U.S. Patent No. 6,277,975.

The –059 patent teaches a conjugate of GPIb fragment that is defective in a transmembrane site and a lipid (see patented claim 13 in particular), wherein the GPIb fragment is a GPIbα chain or GPIbα chain fragment (see patented claim 14), wherein the GPIb a chaing fragment is His(1)-Ala(302), His(1)-Arg(293), His(1)-Ala(302) wherein Gly(233) is substituted by Val or His(1)-Ala(302) wherein Met(239) is substituted by Val (see patented claim 27 in particular). The `059 patent further teaches a substituted compound is exemplified by GPIb a chain fragments consisting of His(1)-Ala(302), wherin Gly (233) and Met(239) are respectively substituted by Vla (see col., 2, lines 65-67 in particular). The `059 patent teaches the use of GPIb conjugate as a pharmaceutical agent as a platelet substitute, a pharmaceutical product for the prophylaxis and treatment of angiopathy, vascular damages and thrombosis, a diagnostic for vWF deficiency and the like, a biological or medical reagent, a reagent for screening platelet aggregation suppressant or anti-thrombosis (see col., 6, line 49 and col., 7, lines 61-67 in particular). The `059 patent teaches that the GPIB-conjugate can be embodied as a diagnostic of Von Willebrand deficiency (see col., 6 line 50 in particular). Furthermore, the `059 teaches the use of the GPIbα as a vehicle of a hemostatic agent, vasoconstrictor, anti-inflammatory agent, fibrinolytic agent, anti-blood coagulator or anti-platelet agent. (see col., 7, lines 17-23 in particular).

The claimed invention differs from the reference teachings only by the recitation of that the fusion protein, wherein said first polypeptide is more resistant to proteolysis than a wild-type GP Ibα1 polypeptide in claim 6, wherein the said second polypeptide comprises an Fc region of an immunoglobulin heavy chain in claim 11, wherein said second polypeptide has less effector function that the effector function of a Fc region of a wild-type immunoglobulin heavy chain in

claim 12, wherein said second polypeptide binds with low or no affinity to a Fc receptor in claim 13, wherein said second polypeptide binds with low or no affinity to complement protein C1q in claim 14, a multimeric polypeptide comprising the fusion protein in claim 21, wherein the multimeric polypeptide is a dimmer in claim 22. wherein the first polypeptide binds at least three polypeptides selected from leukocyte integrin Mac-1 polypeptide, von Willebrand factor, thrombin and p-selectin in claims 54, wherein the firs polypeptide binds leukocyte integrin Mac-1 polypeptide, von Willebrand factor, thrombin and P-selectin in claim 55, wherein said first polypeptide binds leukocyte integrin Mac-1 polypeptide in claim 56, wherein said first polypeptide binds von Willebrand factor in claim 57, wherein said first polypeptide binds thrombin in claim 58, wherein said first polypeptide binds P-selectin in claim 59.

The `975 patent teaches the P-selectin ligand fusion protein comprises a 313 amino acid sequence (see reference SEQ ID NO: 36 in particular) comprising Fc portion of a human of IgGγ1 (column 11, lines 40-41 in particular) with 100% homology with amino acids 318-544 of claimed SEQ ID NO: 1 (see sequence alignment in particular). The `975 patent further teaches that Fc portion of native or mutated immunoglobulin sequences for conferring desirable qualities such as longer half-life or reduced immunogenicity (see column 10 lines 37-40 in particular). Finally, the `975 patent teaches pharmaceutical compositions comprising the P-selectin ligand proteins (column 4, lines 48-50 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the lipid taught by the `059 patent with Fc portion of a human IgGγ1 taught by the `975 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the conjugate can be used as a platelet substitute, a pharmaceutical product for the prophylaxis and treatment of angiopathy, vascular damages and thrombosis, a diagnostic for vWF deficiency and the like, a biological or medical reagent, a reagent for screening platelet aggregation suppressant or anti-thrombosis as taught by the `059 patent. Further, Fc portion of native or mutated immunoglobulin sequences conferring desirable qualities such as longer half-life or reduced immunogenicity as taught by the `972 patent.

Claim 6 is included because the claimed and reference first polypeptide are the same in the absence of evidence to the contrary and therefore, the claimed limitation of more resistant to proteolysis than wild-type GPIbα1 polypeptide is considered inherent properties.

The claimed functional limitation of claims 12-14, 21-22 would be expected properties of the referenced Fc region of a human of IgGγ1 because the claimed and reference Fc region are 100% identical. Further, binding of the first polypeptide to leukocyte integrin Mac-1 polypeptide, von Willebrand factor, thrombin and P-selectin of claims 54-59 is inherent property of the 1st polypeptide. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. Claims 1, 5, 20 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miura *et al* (J Biol Chem. 275:7539-7546) or USP 6,177,059 each in view of U.S. Patent No. 6,277,975 as applied to claims 1, 3, 6-9, 11-14, 21-22, 27, 54-60 above, and further in view of U.S Patent No. 5,340,727.

The teachings of Miura *et al* reference and the `975 patent, has been discussed, supra.

The claimed invention differs from the reference teachings only by the insertion of a signal peptide MPLLLLLLLLPSPLHP which result in SEQ ID NO:1 and 5 in claims 5, 20 and 63-66.

The `727 patent teaches that the predicted GPIba sequence consists of a 16 amino acid signal peptide, $MET^{-16}$ through $PRO^{-1}$, followed by a 610 amino acid mature peptide region, $HIS^{1}$ through $LEU^{610}$ amino acid (see column 2 lines 39-49 in particular). The `727 patent further teaches that the signal peptide when attached to the amino terminal end of the residue 1-610 or 1-302 GPIbα polypeptide, the signal peptide causes the polypeptide to be recognized by cellular structures as a polypeptide of the kind to be processed for ultimate secretion from the cell, with concomitant cleavage of the signal polypeptide from the mature GPIbα polypeptide (column 14 lines 52-64 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to insert the signal peptide taught by the `727 patent in the amino terminal end of the 1-289 GPIbα polypeptide taught by Miura *et al* or `059 patent and then link the resultant GPIbα polypeptide with the Fc portion of a human IgGγ1 taught by the `975 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the signal peptide causes the polypeptide to be recognized by cellular structures as a polypeptide of the kind to be processed for ultimate secretion from the cell, with concomitant cleavage of the signal polypeptide from the mature GPIbα polypeptide as taught by the `727 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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